

## LEADING ARTICLE

## The IL23 axis plays a key role in the pathogenesis of IBD

Dermot McGovern, Fiona Powrie

Exciting new results from a genetic study in humans and functional studies in mice have pinpointed interleukin 23 (IL23) and its receptor as a key pathway in the pathogenesis of inflammatory bowel disease (IBD). These findings reveal a hitherto unappreciated role for the IL23 axis in intestinal inflammation and may open new avenues for development of therapeutic strategies in IBD.

Over the last decade, mouse models of intestinal inflammation have provided invaluable tools to identify cytokines that drive the inflammatory response. Amongst these interleukin 12 (IL12), through its capacity to promote T helper type 1 (Th1) responses, emerged as a pivotal player in the development and perpetuation of colitis.<sup>1</sup>

Genetic deletion or antibody-mediated neutralisation of IL12 led to amelioration of intestinal inflammation in a number of different models.<sup>2–3</sup>

However, the functional role of IL12 has been re-evaluated with the discovery in 2000 of a related cytokine IL23.<sup>4</sup> IL12 is a heterodimeric cytokine composed of a p40 and p35 subunit, whereas IL23, also a heterodimer, is composed of a unique p19 chain linked to the p40 subunit. Many of the reagents used to assess the role of IL12 are directed against the shared IL12/IL23 p40 molecule, meaning that activities previously ascribed to IL12 may have been mediated via IL23.

The development of neutralising anti-IL23 p19 monoclonal antibodies and IL23-deficient mice enabled investigators to distinguish between the activities of IL12 and IL23 and, in 2006, four reports identified IL23 but not IL12 as an essential mediator of intestinal inflammation.<sup>5–8</sup> In those studies, IL23 was found to orchestrate an inflammatory cytokine cascade involving increased levels of tumour necrosis factor  $\alpha$  (TNF $\alpha$ ), IL6, interferon  $\gamma$  (IFN $\gamma$ ) and IL17 in the intestine (fig 1). Similar results were also found in models of brain<sup>9</sup> and joint inflammation,<sup>10</sup> suggesting that IL23 is an important conductor of the inflammatory response in tissues.

The next question is how IL23 mediates intestinal inflammation. The functional IL23 receptor (IL23R) is a heterodimer of the IL12R $\beta$ 1 subunit, which is shared with the IL12 receptor and a novel IL23R subunit which is expressed by activated T cells and myeloid cells. To date, attention has focused on the ability of IL23 to promote a novel subset of IL17-producing CD4<sup>+</sup> T cells termed Th17 cells.<sup>11–13</sup> These cells are distinct from Th1 and Th2 cells, and recent evidence in the mouse indicates that transforming growth factor  $\beta$  (TGF $\beta$ ) and IL6

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drive the differentiation of Th17 cells from naïve T cells.<sup>14</sup> TGF $\beta$  and IL6 induce IL23R expression on Th17 cells, rendering them responsive to IL23.<sup>15</sup> Accumulation of Th17 cells is reduced in the absence of IL23, suggesting that IL23 may maintain or stabilise the Th17 response.<sup>7–8–16</sup> IL17 is a pleiotropic cytokine that acts on both immune and non-immune cells and is increased in the intestine of IBD patients.<sup>17</sup> IL17 can activate stromal, endothelial and epithelial cells to produce cytokines and chemokines, leading to increased neutrophil recruitment into tissues, and also induces inflammatory cytokine production by macrophages.<sup>18</sup> Although IL17 has been shown to play an important role in IL23-driven central nervous system inflammation,<sup>16–19</sup> its role in intestinal inflammation is less pronounced. Neutralisation of IL17 was not sufficient to inhibit colitis in IL10-deficient mice and was only partially protective when combined with anti-IL6 therapy, suggesting that in the intestine IL23 drives IL17-independent inflammatory pathways.<sup>5</sup>

#### Activities previously ascribed to IL12 may have been mediated via IL23

This may be explained by the recent work of Hue *et al*<sup>8</sup> and Uhlig *et al*<sup>6</sup> which has uncovered a novel role for IL23 in controlling innate immunity in the intestine. In these studies, T cell-independent colitis following intestinal bacterial infection or stimulation of the CD40 pathway was found to be dependent on IL23 and not IL12. IL23 is produced by activated myeloid cells including macrophages and dendritic cells (DCs) following bacterial stimulation<sup>20</sup> or via CD40 signalling,<sup>6</sup> and drives increases in a number of inflammatory cytokines in the intestine in the absence of T cells, including TNF $\alpha$ , IFN $\gamma$ , IL6 and IL17. The IL23R is expressed by activated DCs and macrophages, and IL23 can induce production of inflammatory cytokines by macrophages.<sup>9</sup> These results suggest that an important function of IL23 may be to drive an autocrine loop within the innate immune system, leading to the production of a number of inflammatory mediators that contribute to the intestinal inflammatory response.

So is there really no role for IL12- and IFN $\gamma$ -producing Th1 cells in chronic intestinal inflammation? In models of autoimmune disease there is evidence that IL12 and IFN $\gamma$  antagonise the

**Abbreviations:** DC, dendritic cell; IBD, irritable bowel disease; IFN $\gamma$ , interferon  $\gamma$ ; IL, interleukin; IL23R, interleukin 23 receptor; SNP, single-nucleotide polymorphism; TGF $\beta$ , transforming growth factor  $\beta$ ; Th, T helper; TNF $\alpha$ , tumour necrosis factor  $\alpha$

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into disease pathogenesis and highlights potential avenues for future therapeutic intervention in IBD (see later).

**Mouse and human studies highlight the IL23–IL23R axis as a target for development of novel therapies for IBD.**

Two other non-synonymous (amino acid changing) *IL23R* SNPs were identified in this study, but showed no association with IBD. A number of *IL23* intronic variants were shown to be associated with susceptibility to IBD, and the authors have speculated that these variants may occur at splicing sites and so lead to *IL23R* splice variants (that are known to exist) which may alter protein function. The arginine residue encoded by the 381 codon of *IL23R* is the fifth amino acid in the cytoplasmic domain of the receptor and is highly conserved across species, suggesting that this residue plays a crucial role in the function of the receptor. However, no 'functional' data regarding the effect of this polymorphism or the other associated variants on the normal *IL23* pathway were presented in the paper. The functional studies will be eagerly awaited to see if these variants lead to a 'gain of' or 'loss of' function within this pathway—an unresolved debate that continues about the effect of the *NOD2* (*CARD15*) variants 5 years after their identification!<sup>29–31</sup> Replication studies by independent groups are also necessary (although the reproduction of the finding in two independent cohorts provides convincing evidence of a 'true' association) and it will also be interesting to see the results from non-Caucasian cohorts as the published data suggest that some IBD susceptibility loci are 'shared' by different ethnic groups<sup>23</sup> whereas others are not.<sup>32–33</sup>

**An IL12 p40 monoclonal antibody that neutralises IL12 and IL23 may be an effective treatment for Crohn's disease**

The genetic data complement the functional data in mice and provide a compelling case for further analysis of the *IL23*-dependent inflammatory response in the intestine. A considerable amount of research is needed to assess the role of *IL23R* variants in other ethnic groups and to ascertain whether there is any epistasis (interaction) between these variants and other susceptibility genes and environmental risk factors for IBD; furthermore, large-scale studies are needed to ascertain the clinical consequences of these variants. Most pressing, however, is the need for an understanding of the functional effects of *IL23R* variants on the *IL23* pathway.

The mouse and human studies highlight the *IL23*–*IL23R* axis as a target for development of novel therapies for IBD. Both *IL12* and *IL23* are increased in the intestine of patients with Crohn's disease, and there are encouraging data from early study findings that an *IL12* p40 monoclonal antibody that neutralises *IL12* and *IL23* may be an effective treatment for Crohn's disease.<sup>34</sup> Indeed, the best option in terms of controlling the inflammatory response may be to block the activities of both *IL12* and *IL23*. However, *IL12*-dependent responses such as Th1 and cytotoxic T cell responses play a key role in host protective immunity, and blockade of these may leave patients vulnerable to infection and cancer. The study by Uhlig *et al.*<sup>6</sup> directly addressed the roles of *IL12* and *IL23* in systemic and mucosal innate immunity and showed that anti-CD40-induced systemic inflammation was dependent on *IL12* and not *IL23*, whereas the inverse was true for intestinal inflammation. These results suggest that targeting *IL23* may allow a more selective block of the tissue inflammatory response while sparing systemic immunity. However, there is evidence that *IL23* contributes to antibacterial immunity at mucosal surfaces,<sup>15–35</sup> and further understanding of this pathway will be required to

balance the beneficial effects of *IL23* depletion on chronic inflammation with potential deleterious effects on host protective mucosal immunity.

The convergence of two widely different experimental approaches on the *IL23* pathway as a key regulator in the development of intestinal inflammation is an exciting advance in IBD research. Clearly many questions remain to be answered before these results will be translated into better therapies for patients with IBD; however, this potential makes the effort worthwhile.

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## EDITOR'S QUIZ: GI SNAPSHOT .....

### Multiple liver lesions in a smoker

Robin Spiller, Editor

#### Clinical presentation

A 39-year-old female smoker presented to the gastrointestinal unit with a 6-month history of increasing right upper quadrant pain, abdominal distension, nausea and anorexia. There was a history of dysmenorrhoea but no bowel disturbance. There was no medical history of note.

On examination, the abdomen was distended with right upper quadrant tenderness. Investigations showed a normal full blood count and normal renal and liver biochemistry. Inflammatory and tumour markers were not elevated. An



Figure 1 CT scan of the abdomen.

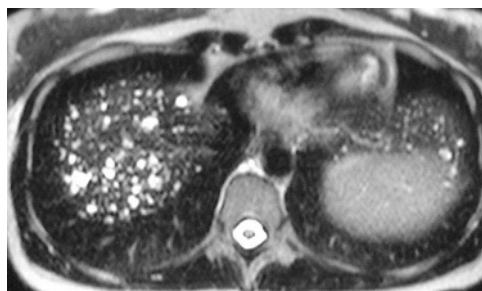


Figure 2 Axial T2-weighted MRI scan of the abdomen.

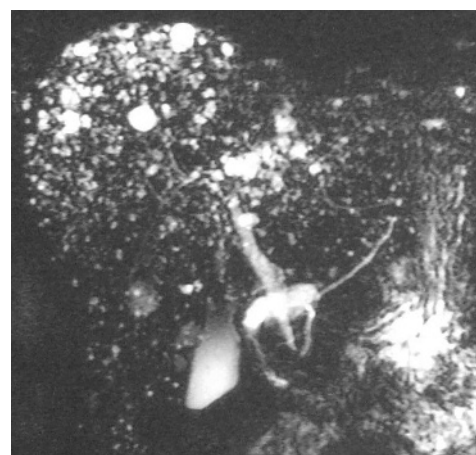


Figure 3 Coronal T2-weighted MRI scan of the liver.

abdominal ultrasound identified an enlarged liver with coarse echo texture and several focal abnormalities throughout both lobes. A CT scan of the abdomen showed multiple indeterminate areas of low attenuation within the liver (figure 1). MRI of the liver (figures 2, 3) provided further characterisation.

#### Question

What is the diagnosis and what further investigation and follow-up is needed?

See page 1352 for answer

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